

Electronic Acknowledgement Receipt

Exhibit B

EFS ID:	2069664
Application Number:	10758939
International Application Number:	
Confirmation Number:	6534
Title of Invention:	Methods of modulating IL-6
First Named Inventor/Applicant Name:	Stephen John Carter
Correspondence Address:	Nabeela R. McMillian MARSHALL, GERSTEIN & BORUN LLP 233 S. Wacker Drive, Suite 6300 Sears Tower Chicago IL 60606-6357 US -
Filer:	Nabeela Rasheed McMillian
Filer Authorized By:	
Attorney Docket Number:	28594/41530
Receipt Date:	10-AUG-2007
Filing Date:	15-JAN-2004
Time Stamp:	11:12:11
Application Type:	Utility under 35 USC 111(a)

Payment information:

Submitted with Payment	yes
Payment was successfully received in RAM	\$60
RAM confirmation Number	5620

The Director of the USPTO is hereby authorized to charge indicated fees and credit any overpayment as follows:
Charge any Additional Fees required under 37 C.F.R. Section 1.16 and 1.17

File Listing:

Document Number	Document Description	File Name	File Size(Bytes) /Message Digest	Multi Part /.zip	Pages (if appl.)
1	Extension of Time	EOT.pdf	25660	no	1
			2082e728a6f79135384525ed33a6706 90d8a2		
Warnings:					
Information:					
2		R2OA.pdf	51529	yes	6
			3ee1e4ad897428637c1e2323477221c 939c34614		
	Multipart Description/PDF files in .zip description				
	Document Description		Start	End	
	Amendment - After Non-Final Rejection		1	1	
	Claims		2	2	
	Applicant Arguments/Remarks Made in an Amendment		3	6	
Warnings:					
Information:					
3	Rule 130, 131 or 132 Affidavits	Williamsdec.pdf	1060759	no	22
			145f9699621670b0a52bbae3387be66b 00410a2		
Warnings:					
Information:					
4	Fee Worksheet (PTO-06)	fee-info.pdf	8132	no	2
			7a854c56a82ba15e1a678f533a00af 79a3706		
Warnings:					
Information:					
Total Files Size (in bytes):			1146080		

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New Applications Under 35 U.S.C. 111

If a new application is being filed and the application includes the necessary components for a filing date (see 37 CFR 1.53(b)-(d) and MPEP 506), a Filing Receipt (37 CFR 1.54) will be issued in due course and the date shown on this Acknowledgement Receipt will establish the filing date of the application.

National Stage of an International Application under 35 U.S.C. 371

If a timely submission to enter the national stage of an international application is compliant with the conditions of 35 U.S.C. 371 and other applicable requirements a Form PCT/DO/EO/903 indicating acceptance of the application as a national stage submission under 35 U.S.C. 371 will be issued in addition to the Filing Receipt, in due course.

New International Application Filed with the USPTO as a Receiving Office

If a new international application is being filed and the international application includes the necessary components for an international filing date (see PCT Article 11 and MPEP 1810), a Notification of the International Application Number and of the International Filing Date (Form PCT/RO/105) will be issued in due course, subject to prescriptions concerning national security, and the date shown on this Acknowledgement Receipt will establish the international filing date of the application.

PETITION FOR EXTENSION OF TIME UNDER 37 CFR 1.136(a) FY 2006 (Fees pursuant to the Consolidated Appropriations Act, 2005 (H.R. 4818).)		Docket Number (Optional) 28594/41530	
Application Number 10/758,939-Conf. #6534		Filed January 15, 2004	
For METHODS OF MODULATING IL-6			
Art Unit 1623		Examiner Elli Peselev	
This is a request under the provisions of 37 CFR 1.136(a) to extend the period for filing a reply in the above identified application. The requested extension and fee are as follows (check time period desired and enter the appropriate fee below):			
		<u>Fee</u>	<u>Small Entity Fee</u>
<input checked="" type="checkbox"/> One month (37 CFR 1.17(a)(1))		\$120	\$60 \$ 60.00
<input type="checkbox"/> Two months (37 CFR 1.17(a)(2))		\$450	\$225 \$
<input type="checkbox"/> Three months (37 CFR 1.17(a)(3))		\$1020	\$510 \$
<input type="checkbox"/> Four months (37 CFR 1.17(a)(4))		\$1590	\$795 \$
<input type="checkbox"/> Five months (37 CFR 1.17(a)(5))		\$2160	\$1080 \$
<input type="checkbox"/> Applicant claims small entity status. See 37 CFR 1.27. <input type="checkbox"/> A check in the amount of the fee is enclosed. <input type="checkbox"/> Payment by credit card. Form PTO-2038 is attached. <input type="checkbox"/> The Director has already been authorized to charge fees in this application to a Deposit Account. <input checked="" type="checkbox"/> The Director is hereby authorized to charge any fees which may be required, or credit any overpayment, to Deposit Account Number <u>13-2855</u> . I have enclosed a duplicate copy of this sheet.			
I am the <input type="checkbox"/> applicant/inventor. <input type="checkbox"/> assignee of record of the entire interest. See 37 CFR 3.71. <input checked="" type="checkbox"/> attorney or agent of record. Registration Number <u>43,363</u> <input type="checkbox"/> attorney or agent under 37 CFR 1.34. Registration number if acting under 37 CFR 1.34 _____			
<u>/Nabeela R. McMillian/</u> Signature <u>Nabeela R. McMillian</u> Typed or printed name		<u>August 10, 2007</u> Date <u>(312) 474-6300</u> Telephone Number	
NOTE: Signatures of all the inventors or assignees of record of the entire interest or their representative(s) are required. Submit multiple forms if more than one signature is required, see below.			
<input type="checkbox"/> Total of <u>1</u> forms are submitted.			

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted via the Office electronic filing system in accordance with § 1.6(a)(4).

Dated: August 10, 2007

Signature: /Nabeela R. McMillian, #43,363/

(Nabeela R. McMillian)

I hereby certify that this paper (along with any paper referred to as being attached or enclosed) is being transmitted by facsimile to the Patent and Trademark Office, facsimile no. (571) 273-8300, on the date shown below.

Dated: August 10, 2007

Signature: /Nabeela B. McMillan/
(Nabeela R. McMillan)

Docket No.: 28594/41530
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Stephen Carter et al.

Application No.: 10/758,939

Confirmation No.: 6534

Filed: January 15, 2004

Art Unit: 1623

For: METHODS OF MODULATING IL-6

Examiner: Elli Peselev

AMENDMENT AFTER NON-FINAL ACTION DATED APRIL 13, 2007

MS AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

INTRODUCTORY COMMENTS

In response to the Office Action dated April 13, 2007, please amend the above-identified U.S. patent application as indicated below. The present amendment is provided with a petition and fee for a one month extension of time to respond and as such is timely filed.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 3 of this paper.

AMENDMENTS TO THE CLAIMS

Prior to further examination please amend the claims as follows. The following list of claims replaces all prior listings and versions of claims in the specification.

1-52. (Canceled)

53. (Currently amended) A method for treating psoriasis comprising administering to a patient in need thereof a composition consisting essentially of two glycoalkaloids selected from the groups consisting of solamargine, solasonine, solanine, tomatine, solanocapsine and 26-aminofurostane and wherein the two glycoalkaloids are present in the composition at a ratio of between: 1:4 and 1:1 wherein the composition is essentially free of mono- or diglycosides, free sugars and aglycones of said two glycoalkaloids and said composition has an effect that is potentiated as compared to BEC.

54. (Canceled)

55. (currently amended) The method of claim 53 wherein the glycoalkaloids are solamargine and ~~solasine~~ solasonine.

56. (Canceled)

57. (Previously presented) The method of claim 53 wherein the ratio of glycoalkaloids is between about 1:1.

58-78. (Canceled)

79. (New) The method of claim 53 wherein the ratio of solamargine:solasonine is between about 1:1.

REMARKS

I. Status of the Claims

Claims 53, 55 and 57 were rejected under 35 U.S.C. § 103(a) over Cham et al. (Australian Patent No. 57853/80). Applicants respectfully request reconsideration of the rejection in view of the following remarks and the above amendment.

Claim 53 has been amended to expressly clarify that the composition used in the methods is "essentially free of mono- or diglycosides, free sugars and aglycones of said two glycoalkaloids and said composition has an effect that is potentiated as compared to BEC." This amendment is supported by the disclosure at page 7, lines 20-22 of the specification.

New claim 79 is presented in order to claim dependency from claim 55 which was inadvertently removed in the prior amendment.

II. The rejection under 35 U.S.C. § 103 (a) over Cham et al. should be withdrawn.

The examiner rejected claims 53, 55 and 57 under 35 U.S.C. § 103 (a) over Cham et al. (Australian Patent No. 57853/80). Applicants respectfully request reconsideration of the rejection in view of the amendments made herein and the following remarks.

Applicants previously noted that Cham et al. discloses a composition that comprises solasonine (as 33% of the composition) and solamargine (as 33% of the composition), the composition also includes a third portion which was made up of di- and mono-glycosides and free sugar (rhamnose). The composition recited in independent claim 53 does not include this third portion. Further, Applicants pointed out that the Cham et al. document provided a teaching of BEC which is a plant extract containing solarmarine, solasonine, their corresponding mono and di-glycosides, free sugars and aglucone.

In the present office action, the Examiner noted that Cham et al. at page 17 does not require the presence of di- and mono-glycosides and free sugar. Applicants

respectfully submit that the entire teaching of Cham et al. is directed to a general plant extract and not an isolated composition that contains essentially the two active ingredients being recited in the present claims. While there is a general open-ended claim at page 17 of Cham et al. the entire enablement in that specification is directed to use of just the plant extract. Moreover, the statement at page 17 of the Cham et al requires only one active component, without making any reference to the potency of such an active compound. The entire Cham et al. document provides no indication whatsoever that the presence of two glycoalkaloids together, without the presence of free sugars and aglycones has a potentiated effect as compared to the plant extract. Applicants have amended claim 53 to clarify that the claimed composition *requires only the two glycoalkaloids* as active ingredients and further that the composition is more effective as compared to a composition that contains the plant extract BEC.

As further evidence that the compositions used in the currently claimed methods, attached herewith a declaration from Dr. Elizabeth Williams (*originally filed in related application U.S. Serial No. 11/143,043, which is a related case*) which provides objective evidence of the efficacy and effectiveness of the presently claimed 2-glycoside component compositions as compared to BEC, the composition that is described in the Cham document. The declaration of Dr. Williams is based on data that she generated in experiments performed *circa* November 2001 and February 2002.

As noted by Dr. Williams, the BEC composition that she used was supplied by Dr. Cham (Williams Declaration ¶5). Dr. Williams performed cytotoxicity studies using BEC, solamargine and solasonine and obtained data that establishes that solamargine is considerably more potent than solasonine at killing cells (Williams Declaration ¶6). Moreover Dr. Williams shows that there is “a synergistic effect between solamargine and solasonine at the level of intracellular effect, and that BEC is not as effective as a 1:1 mixture of solasonine and solamargine alone.” (Williams Declaration ¶6).

In the data shown and discussed in Williams Declaration ¶10, a BEC preparation was compared with a 1:1 mixture of purified solamargine and solasonine, and also compared to purified preparations of each of solamargine and solasonine under conditions in which receptor affinity is the predominant determinant of LD₅₀. From these

data, Dr. Williams concluded that solamargine has a higher affinity than solasonine for the cell surface receptor that mediates uptake by cells (Williams Declaration ¶11a). Further, the data support the finding of the synergistic properties of solasonine and solamargine at the point of uptake into the cell (Williams Declaration ¶11b). Importantly, these data also lead to the conclusion that the BEC composition (i.e., the composition described in Cham) is not as effective as the isolated 1:1 solamargine:solasonine mixture (Williams Declaration ¶11b).

In another set of experiments, Dr. Williams compared the effects of a BEC preparation with the effects of a 1:1 mixture of purified solamargine and solasonine or purified preparations of each of solamargine and solasonine under conditions in which the dose per cell was limiting for cytotoxic effect (Williams Declaration ¶12). These studies showed that solamargine is considerably more potent than solasonine at killing cells (Williams Declaration ¶13a) and that solamargine and solasonine have a synergistic effect at the intracellular level. Again, BEC was found to be not as effective as the isolated 1:1 solamargine:solasonine mixture (Williams Declaration ¶13b). Dr. Williams concludes that “the BEC composition is not as effective at cell killing or being taken up by the cells as a composition that consists of a 1:1 ratio of solamargine:solasonine.” (Williams Declaration ¶14).

In view of the above amendments and remarks, applicants submit that the claims as presented above are non-obvious. Accordingly, the rejections should be withdrawn.

III. Conclusion

For the foregoing reasons, applicants request withdrawal of all outstanding rejections and allowance of the pending claims. No other fees are believed to be due with the filing of this paper. However, the Director is authorized to charge any additional fees deemed necessary to Deposit Account No. 13-2855, under order number 28594/41530.

If the examiner believes that a telephone conversation would expedite allowance of the claims, she is invited to contact the undersigned at the number below.

Dated: August 10, 2007

Respectfully submitted,

By /Nabeela R. McMillian, #43,363/
Nabeela R. McMillian,
Registration No.: 43,363
MARSHALL, GERSTEIN & BORUN LLP
233 S. Wacker Drive, Suite 6300
Sears Tower
Chicago, Illinois 60606-6357
(312) 474-6300
Agent for Applicant

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: Williams *et al.*

Application No.: 11/143,043

Group Art Unit: 1623

Confirmation # 8801

Filed: June 2, 2005

Examiner: Elli Peselev

For: GLYCOALKALOID COMPOSITIONS AND
VARIOUS USES THEREOF

DECLARATION UNDER 37 C.F.R. § 1.132 OF DR. ELIZABETH WILLIAMS

Commissioner for Patents
P.O. Box 1450,
Alexandria, Virginia 22313-1450

Dear Sir:

I, Dr. Elizabeth Williams, do hereby declare and state as follows:

1. I am an inventor on the above-identified U.S. patent application (hereinafter, the "patent application"). I am a scientist, previously working at the Centre for Applied Cancer Studies in University of Western Australia. I am now working as a technical proofreader/editor for SRK Consulting Pty Ltd. I have a Ph.D. in Agricultural Science. A copy of my curriculum vitae is attached as Exhibit A.

2. I am familiar with the contents of patent application and with the official action from the United States Patent and Trademark Office (hereinafter, the "Patent Office") dated December 19, 2006, a copy of which is attached hereto as Exhibit B. A copy of the claims that I understand are pending in the reference application are attached hereto as Exhibit C.

3. In reviewing the Office action, I understand that by reciting the term "consisting essentially of" and by reciting the term "and is substantially free of mono- and diglycerides and free rhamnose" each of the claims that are attached in Exhibit C exclude mono-

and diglycerides and free rhamnose and also exclude any other materials that will affect the activity or characteristics of the composition being claimed.

4. However, I note that having stated the above, at page 3 of the Office action the Examiner has indicated that the above argument is "not persuasive" and that "[t]he has not pointed how the amount of the di- and mono-glycosides in the composition disclosed by Cham differs from the amount of said glycosides in the claimed compositions." I am providing the following remarks and description of data in order to provide evidence that glycoalkaloid compositions that contain di- and mono-glycosides and rhamnose are not as effective as the compositions that are substantially free of such components.

5. I am familiar with WO 91/10743, WO 00/6153 and AU-B-57853/80 (referred to herein as "the Cham documents"). It is my belief that the Cham documents relate to a composition known as BEC, which is a composition that contains solasonine, solamargine and di- and mono-glycosides and free sugar (rhamnose). I have performed experiments using BEC, and I describe these experiments below. I understand from discussions with Dr Carol Worth, Senior Scientist / Quality Manager at Solbec Pharmaceuticals Ltd (referred to herein as "Solbec"), that the BEC with which I was supplied and used for my studies was in turn supplied to Solbec by Dr Cham.

6. I am making this declaration in order to provide facts relating to properties of the compositions claimed in the subject application. In particular, I have performed cytotoxicity studies of BEC, solamargine and solasonine and have evidence that establishes that solamargine is considerably more potent than solasonine at killing cells; that there is a synergistic effect between solamargine and solasonine at the level of intracellular effect, and that BEC is not as effective as a 1:1 mixture of solasonine and solamargine alone.

7. BEC is the composition of the Cham documents. BEC is a crude preparation of glycoalkaloids that includes a substantial amount of di- and mono-glycosides and free rhamnose and other plant products. The crude BEC preparation of the Cham documents had a brown colour. It is my understanding, again from discussions with Dr Carol Worth, that this brown coloration of BEC is partly due to the Maillard reaction and partly due to the quantity of co-extracted plant material, including phenolics which readily brown in air.

8. I performed original assays of BEC cytotoxicity in order to compare the effects a crude preparation on a range of cell lines derived from a variety of different cancerous tumours and from primary non-cancerous tissues.

9. For any given concentration of BEC, the number of glycoalkaloid molecules available to be taken up by each cell, and to then disrupt cellular processes, is determined directly by the number of cells present. The data for all cell lines was analysed by plotting the measured LD₅₀s as dose of BEC per cell against the number of cells in the population used for each determination. This yielded a bimodal distribution of points. At densities between 500 and 1500 cells per well the points for all cell lines, cancerous and non-cancerous, fell on a near vertical line. At densities between 4000 and 10000 cells per well the points fell on one of two horizontal lines. Points for all cancer cell lines except those derived from breast tumours fell on the lower line, reflecting an approximately three-fold higher sensitivity to BEC than non-cancerous and breast cancer cell lines, the points for which fell on a line three times higher on the Dose per Cell at LD₅₀ axis.

10. A BEC preparation was compared with a 1:1 mixture of purified solamargine and solasonine, together with purified preparations of solamargine and solasonine under conditions in which receptor affinity is the predominant determinant of LD₅₀ the following values were observed for cell line 786-O:

LD ₅₀ , µg/mL total glycoalkaloid			
1. BEC	2. Solamargine	3. Solasonine	4. Solamargine + Solasonine (1:1 mixture)
4.4	4.53	18.22	1.47

11. From the above data, it is my conclusion that:

a. solamargine has a higher affinity for the cell surface receptor that mediates its uptake by cells than solasonine has with the cell surface receptor mediating its entry into cells (compare column 2 with column 3);

b. solasonine and solamargine act synergistically with each other at the point of uptake into the cell, possibly through a co-operative effect between different receptors or through concurrent stimulation of the same receptor (compare column 2 and 3 with the data in column 4); and

c. BEC composition is not as effective as the isolated 1:1 solamargine:solasonine mixture (compare column 1 with column 4).

12. In addition to the data described in paragraph 10 above, experiments were performed in which a BEC preparation was compared with a 1:1 mixture of purified solamargine and solasonine, together with purified preparations of solamargine and solasonine under conditions in which the dose per cell was limiting for cytotoxic effect. This was examined for six different cell lines, including 786-O and showed the following data:

Dose per cell at LD ₅₀ , pg/cell of total alkaloid						
1. Cell line	2. BEC	3. Solamargine	4. Solasonine	5. (1:1 mixture of the two glycoalkaloids)	6. Solamargine in 1:1 mixture	7. Solamargine in BEC
NO36	298.0	154.8	613.2	148.4	74.20	74.50
LNCaP	428.5	121.9	432.5	117.3	58.65	107.13
LS174T	465.2	162.8	>400	171.6	85.80	116.30
A2058	247.0	199.0	685.0	78	39.00	61.75
786-O	321.2	208.0	>400	134.4	67.20	80.30
NHDF-Ad	283.3	209.2	584.0	156.8	78.40	70.83

13. From the above data, it is again my conclusion that:

a. solamargine is considerably more potent than solasonine at killing cells, as can be seen by comparing column 3 with column 4;

b. there is a synergistic effect between solamargine and solasonine at the level of intracellular effect, as can be seen by comparing columns 3 and 4 with column 5; and

c. BEC composition is not as effective as the isolated 1:1 solamargine:solasonine mixture, as can be seen by comparing column 2 with column 5.

14. From the above-reported data, it is my belief that the BEC composition is not as effective at cell killing or being taken up by the cells as a composition that consists of a 1:1 ratio of solamargine:solasonine.

15. I further declare that all statements made herein of my own knowledge are true, that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both (18 U.S.C. § 1001), and may jeopardize the validity of the application or any patent issuing thereon.

Date April 2 2007



Dr. Elizabeth Williams

APPENDIX A: CURRICULUM VITAE OF DR ELIZABETH WILLIAMS

Elizabeth Anne Williams B Agr Sc PhD (Tas) LLB (UWA)

Telephone: (08) 9244 7731 Mobile: 0409 779 043

email: e.a.williams@bigpond.com

CURRICULUM VITAE

PERSONAL DETAILS:

Name Elizabeth Anne Williams (nee Stronach)

Address 5 Craig Street, Wembley Downs, WA 6019

Nationality Australian citizen

EDUCATION:

1975 Admitted to degree of B Agr Sc (University of Tasmania)

1989 Admitted to degree of Ph D (University of Tasmania)

1998 Awarded Advanced Certificate in Principles of Protein Structure (University of London)

2006 Admitted to degree of LLB, (University of Western Australia)

2006- Currently studying for Graduate Diploma in Legal Practice with The College of Law, Sydney, NSW.

SCHOLARSHIPS:

1969-70 Australian Government Secondary Scholarship

1971-74 Australian Government University Scholarship

1971-74 Australian Agricultural Council Scholarship

EMPLOYMENT:

- 1975-77, 1979-1982, and 1985-86** Research Assistant, Faculty of Agricultural Science, University of Tasmania
- 1987-1989** Research Assistant to Dr AB Roy, John Curtin School of Medical Research, Australian National University
- 1989-1991** Postdoctoral Research Fellow with Professor JF Morrison John Curtin School of Medical Research, Australian National University
- 1992** Independent Postdoctoral Research Fellow, John Curtin School of Medical Research, Australian National University; and
Research Associate, Research School of Biological Science, Australian National University
- 1993-96** Research Fellow and Laboratory Head, Lions Cancer Institute of Western Australia
- 1996-2002** Research Fellow and Laboratory Head, Centre for Applied Cancer Studies, University of Western Australia
- 1998-1999** Deputy Director, Centre for Applied Cancer Studies, University of Western Australia
- 1999-2003** Director, Centre for Applied Cancer Studies, University of Western Australia
- 2007** Technical Proofreader/Editor, SRK Consulting Engineers and Scientists

PROFESSIONAL MEMBERSHIPS:

- 1989-2003** Australian Society for Biochemistry and Molecular Biology
- 1993-2003** Australian Society for Medical Research
- 2005-** Student member of LEADR, Association of Dispute Resolvers

PROFESSIONAL COMMITTEE MEMBERSHIPS:

- 1992 Australian National University Staff Association
- 1992-93 National Research Policy Committee of the National Tertiary Education Union

SOME PAST EXTRA-CURRICULAR INTERESTS:

- 1979-82 Home tutoring Vietnamese refugees in English language through the Migrant Education Centre
- 1984-85 Fundraising for Bandung International School, Indonesia

CURRENT EXTRA-CURRICULAR INTERESTS:

- 1993-2006 Race control as Starter at Nedlands Yacht Club
- 2005 Coach, Schools Conflict Resolution and Mediation Competition, initiative of the Western Australian Dispute Resolution Association
- 1996- Rotary
- 1975- Occasional bushwalking
- 2005 Role player for LEADR Mediator accreditations

ARTICLES PUBLISHED IN INTERNATIONAL REFEREED JOURNALS

1. Menary, R. C., Williams, E. A. & Doe, P. E. (1983) Enzymic degradation of α -acids in hops. *Journal of the Institute of Brewing* **89**, 200-203.
2. Menary, R. C., Nickerson, G. B. & Williams, E. A. (1986) Effect of myrtenol on the rate of oxidation of α - and β -acids in hops. *Acta Horticulturae* **188**, 149-156.
3. Williams, E. A. & Menary, R. C. (1988) Polyphenolic Inhibitors of α -acid oxidase activity. *Phytochemistry* **27**, 35-39.
4. Williams, E. A. (1989) Inhibition of α -acid oxidase by polyphenolic compounds - a kinetic model. *Phytochemistry* **28**, 1327-1330.
5. Roy, A. B. & Williams, E. A. (1989) The sulphatase from *Helix pomatia*. Purification and kinetic properties. *Comparative Biochemistry and Physiology* **93B**, 229-237.

6. Williams, E. A. & Morrison, J. F. (1991) Characterisation of tightly-bound substrates in pure preparations of dihydrofolate reductase: implications for studies on enzymes. *Biochimica et Biophysica Acta* **1078**, 47-55.
7. Williams, E. A. & Morrison, J. F. (1992) Human dihydrofolate reductase: reduction of alternative substrates, pH effects and inhibition by deazafofolates. *Biochemistry* **31**, 6801-6811.
8. Trapani, J. A., Jans, P., Smyth, M. J., Froelich, C. J., Williams, E. A., Sutton, V. R. and Jans, D. A. (1998) Perforin-dependent nuclear entry of granzyme B precedes apoptosis, and is not a consequence of nuclear membrane dysfunction. *Cell Death and Differentiation* **5**, 488-496.
9. Williams E. A., Hepler, P. K., Carrello, A. C., and John, P. C. L. (1999) Nuclear accumulation kinetics of p9CksHs1 and p9CksHs2 in live plant cells correlate with immunochemical characteristics. *Protoplasma* **209**, 98-105.
10. Kelly J.A., Williams, E. A. and Wilce M. J. C (2005) Preliminary crystallographic analysis of the Cks protein p13^{sup1P90AP92A} from *Schizosaccharomyces pombe*. *European Biophysics Journal* **34**, 430-433.

INVITED LECTURES/SEMINARS

1. Australian Society for Biochemistry and Molecular Biology Mundaring Weir Conference 1993
2. University of Western Australia Biochemistry Department Seminar Series, 1993
3. John Curtin School of Medical Research, Australian National University, 1994
4. Department of Biochemistry, University of Cambridge, Cambridge, U. K., 1994
5. Cell Cycle Control Group, Imperial Cancer Research Fund, London, U. K., 1994
6. TVW Channel 7 Child Health Research Institute Seminar Series, 1995
7. Molecular Genetics and Cell Biology Discussion Group, Royal Perth Hospital, September 1996
8. Cell Cycle Satellite Meeting, Adelaide, 1998
9. Cancer Council Cancer Conference, 2001
10. University of Western Australia Biochemistry Department Seminar Series, 2001

COMPETITIVE RESEARCH GRANTS AWARDED

1993	Royal Perth Hospital Medical Research Foundation
1994	Clive and Vera Ramaciotti Foundations
1995	Cancer Foundation of Western Australia
1995	Institute of Advanced Studies - Australian Universities Collaborative Research Scheme
1996	Lions International Foundation - for establishment of

1998
2001

Molecular Modeling Computer Facility
Royal Perth Hospital Medical Research Foundation
Cancer Foundation of Western Australia



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Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/143,043	06/02/2005	7590 12/19/2006 Nabeela R. McMillian MARSHALL, GERSTEIN & BORUN LLP 233 S. Wacker Drive, Suite 6300 Sears Tower Chicago, IL 60606-6357	28594/41532	8801

RECEIVED

DEC 27 2006

MARSHALL GERSTEIN

EXAMINER

PESELEV, ELLI

ART UNIT	PAPER NUMBER
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1623

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/19/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Docketed: 3-19-07

Office Action Summary

Application No.

11/143,043

Applicant(s)

CARTER ET AL.

Examiner

Eli Peselev

Art Unit

1623

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any entered patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 November 2006.
- 2a) ☒ This action is FINAL. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 54-93 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 54-93 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/06)
Paper No(s)/Mail Date _____

- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 54-94 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Cham (WO 00/61153).

Cham discloses the composition comprising glycoalkaloid composition, wherein essentially all free sugars (page 9, lines 33-38) and aglycones (page 10, lines 24-31) are removed. The claimed compositions are anticipated by Cham. In addition, if there are any differences between the claimed compositions and the prior art's compositions,

the differences would appear to be minor in nature and the claimed compositions, which fall within the scope of the prior art's compositions, would have been *prima facie* obvious from the said reference's disclosure to a person having ordinary skill in the art at the time the claimed invention was made.

Applicant's arguments filed November 21, 2006 have been fully considered but they are not persuasive.

The terminology "consisting essentially of" (claim 54) limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s): if the claimed invention". "If an applicant contends that additional steps or materials in the prior art are excluded by the recitation of "consisting essentially of," applicant has the burden of showing that the introduction of additional steps or components would materially change the characteristics of applicant's invention." (MPEP 2111.03). In the present case Cham discloses removal of any sugars (page 9, lines 33-38) and removal of aglycones (page 10, lines 24-31) from a glycoalkaloid composition. Applicant contends that the Cham reference disclose a composition comprising solasonine (as 33% of the composition) and "solamargine (as 33% of the composition), and a third portion made up of di- and mono-glycosides and free sugar. This argument has not been found persuasive. Applicant has not pointed how the amount of di- and mono-glycosides in the composition disclosed by Cham differs from the amount of said glycosides in the claimed compositions. In the case that there are differences in the amounts, applicant has not provided any evidence that the larger amount of di and mono-glycosides would materially change the characteristics of

the applicant's composition. Further, Cham discloses that the composition "may be formulated from a synthetic glycoalkaloid or a mixture of glycoalkaloids" (page 5, lines 33-38). From the teaching by Cham, a person having ordinary skill in the art at the time the claimed invention was made would have envisaged a synthetic composition of a mixture of glycoalkaloids in the absence of di- and mono-glycosides.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

(A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

(Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elli Peselev whose telephone number is (571) 272-0659. The examiner can normally be reached on 8.00-4.30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Jiang can be reached on (571) 272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Elli Peselev

elli Peselev
ELLI PESELEV
PRIMARY EXAMINER
GROUP 1200

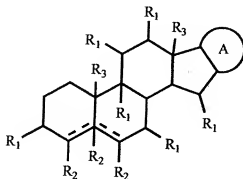
**APPENDIX B: OFFICIAL ACTION FROM THE UNITED STATES PATENT AND
TRADEMARK OFFICE DATED DECEMBER 19, 2006**

APPENDIX C: CLAIMS OF U.S. APPLICATION 11/143,043

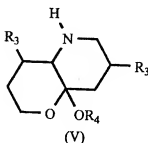
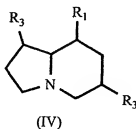
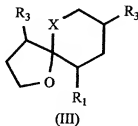
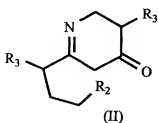
54. [New] A composition consisting essentially of two glycoalkaloids selected from the group of glycoalkaloids consisting of: solamargine, solasonine, solanine, tomatine, solanocapsine and 26-aminofurostane and wherein the two glycoalkaloids are present in the composition at a ratio of between: 1:4 and 1:1.
55. [New] A composition according to claim 54 wherein the glycoalkaloids are solamargine and solasonine.
56. [New] A composition consisting essentially of about a 1:1 ratio of solamargine and solasonine.
57. [New] A composition according to claim 54 or 56 wherein the glycoalkaloids constitute 70%-90% of the composition.
58. [New] A composition according to claim 54 or 56 wherein the glycoalkaloids constitute 91-95% of the composition.
59. [New] A composition according to claim 54 or 56 wherein the glycoalkaloids constitute 96-100% of the composition.
60. [New] A pharmaceutical composition comprising an active ingredient composition consisting essentially of two glycoalkaloids selected from the group of glycoalkaloids consisting of: solamargine, solasonine, solanine, tomatine, solanocapsine and 26-aminofurostane and wherein the two glycoalkaloids are present in the composition at a ratio of between: 1:4 and 1:1 and a pharmaceutically acceptable carrier.
61. [New] A pharmaceutical composition according to claim 60 wherein the glycoalkaloids are solamargine and solasonine.
62. [New] A pharmaceutical composition comprising an active ingredient composition consisting essentially of about a 1:1 ratio of the glycoalkaloids solamargine and solasonine and a pharmaceutically acceptable carrier.
63. [New] The pharmaceutical composition of according to claim 60, 61, or 62 wherein the active ingredient forms between 0.1% to 10% of the pharmaceutical composition.

64. [New] A pharmaceutical composition according to claim 60, 61, or 62, wherein the glycoalkaloids constitute 70%-90% of the active ingredient in the pharmaceutical composition.
65. [New] A pharmaceutical composition according to claim 60, 61, or 62, wherein the glycoalkaloids constitute 91-95% of the active ingredient in the pharmaceutical composition.
66. [New] A pharmaceutical composition according to claim 60, 61, or 62, wherein the glycoalkaloids constitute 96-100% of the active ingredient in the pharmaceutical composition.
67. [New] A pharmaceutical composition according to claim 60, 61, or 62, wherein said composition is a topical delivery composition.
68. [New] A pharmaceutical composition according to claim 60, 61, or 62 wherein said composition is an oral delivery composition.
69. [New] A pharmaceutical composition according to claim 60, 61, or 62 wherein said composition is a parenteral delivery composition.
70. [New] A pharmaceutical composition of claim 63 wherein said composition is a topical delivery composition.
71. [New] A pharmaceutical composition of claim 63 wherein said composition is an oral delivery composition.
72. [New] A pharmaceutical composition of claim 63 wherein said composition is a parenteral delivery composition.
73. [New] A pharmaceutical composition of claim 64 wherein said composition is a topical delivery composition.
74. [New] A pharmaceutical composition of claim 64 wherein said composition is an oral delivery composition.
75. [New] A pharmaceutical composition of claim 64 wherein said composition is a parenteral delivery composition.

76. [New] A pharmaceutical composition of claim 65 wherein said composition is a topical delivery composition.
77. [New] A pharmaceutical composition of claim 65 wherein said composition is a oral delivery composition.
78. [New] A pharmaceutical composition of claim 65 wherein said composition is a parenteral delivery composition.
79. [New] A pharmaceutical composition of claim 66 wherein said composition is a topical delivery composition.
80. [New] A pharmaceutical composition of claim 66 wherein said composition is a oral delivery composition.
81. [New] A pharmaceutical composition of claim 66 wherein said composition is a parenteral delivery composition.
82. [New] A pharmaceutical composition according to claim 63, wherein the glycoalkaloids constitute 70%-90% of the active ingredient in the pharmaceutical composition.
83. [New] A pharmaceutical composition according to claim 63, wherein the glycoalkaloids constitute 91-95% of the active ingredient in the pharmaceutical composition.
84. [New] A pharmaceutical composition according to claim 63, wherein the glycoalkaloids constitute 96-100% of the active ingredient in the pharmaceutical composition.
85. [New] A composition consisting essentially of two glycoalkaloids present in the composition at a ratio of between: 1:4 and 1:1 wherein the composition is essentially free of mono- or diglycosides, free sugars and aglycones, said glycoalkaloids having a formula of:



wherein: either one or both of the dotted lines represents a double bond, and the other a single bond, or both represent single bonds; A: represents a radical selected from the following radicals of general formulae (II) to (V):



each of R^1 is a radical separately selected from the group consisting of hydrogen, amino, oxo and OR^4 ;

each of R^2 is a radical separately selected from the group consisting of hydrogen, amino and OR^4 ;

each of R^3 is a radical separately selected from the group consisting of hydrogen, a carbohydrate and a carbohydrate derivative selected from the group consisting of a glyceric aldehyde, glycerose, erythrose, threose, ribose, arabinose, xylose, lyxose, altrose, allose, gulose, mannose, glucose, idose, galactose, talose, rhamnose, dihydroxyactone, erythrulose, ribulose, xylulose, psicose, fructose, sorbose, tagatose, and other hexoses, heptoses, octoses, nanoses, decoses, deoxysugars with branched chains, sugar alcohols, sugar acids, benzimidazoles, the enol salts of the carbohydrates, saccharinic acids, sugar phosphates;

"X" is a radical selected from the group consisting of $-CH_2-$, $-O-$ and $-NH_2-$; and

wherein the compound includes at least one R^4 group that is a carbohydrate or a carbohydrate derivative selected from the group consisting of glyceric aldehyde, glycerose,

erythrose, threose, ribose, arabinose, xylose, lyxose, altrose, allose, gulose, mannose, glucose, idose, galactose, talose, rhamnose, dihydroxyactone, erythrulose, ribulose, xylulose, psicose, fructose, sorbose, tagatose, and other hexoses, heptoses, octoses, nanoses, decoses, deoxysugars with branched chain, sugar alcohols, sugar acids, benzimidazoles, the enol salts of the carbohydrates, saccharinic acids, sugar phosphates.

86. [New] A composition according to claim 85 wherein the glycoalkaloids constitute 70%-90% of the composition.

87. [New] A composition according to claim 85 wherein the glycoalkaloids constitute 91-95% of the composition.

88. [New] A composition according to claim 85 wherein the glycoalkaloids constitute 96-100% of the composition.

89. [New] A pharmaceutical composition in which the active ingredient consists essentially of the composition of claim 85, 86, 87 or 88 and is substantially free of mono- and diglycerides and free rhamnose.

90. [New] The pharmaceutical composition of 89 wherein said composition is a topical delivery composition.

91. [New] The pharmaceutical composition of 89 said composition is an oral delivery composition.

92. [New] The pharmaceutical composition of 89 said composition is an parenteral delivery composition.

93. [New] The pharmaceutical composition of 89 the active ingredient forms between 0.1% to 10% of the pharmaceutical composition.